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Assessment of cerebral blood flow changes in nonconvulsive status epilepticus in comatose patients: A pathophysiological transcranial Doppler study☆

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ABSTRACT

Purpose: We assessed the accuracy of transcranial Doppler (TCD) in helping to diagnose nonconvulsive status epilepticus (NCSE) in comatose patients admitted to the intensive care unit (ICU) for acute neurological disorders at high risk for NCSE.
Methods: A 2-year prospective observational study in 38 consecutive patients requiring continuous electroencephalography (EEG) monitoring and intracranial pressure monitoring with TCD.
Results: Of the 38 patients, 10 (26.3%) had NCSE by continuous EEG monitoring. Bilateral mean and maximal systolic and diastolic TCD velocities were significantly different between patients with and those without NCSE. Areas under the receiver-operating characteristic (ROC) curves of mean and maximal systolic velocities by TCD were 0.82 (95%CI, 0.64–1.00) and 0.79 (95%CI, 0.62–0.95) with cutoffs of 95 cm/s and 105 cm/s, respectively. Areas under the ROC curves of mean and maximal diastolic velocities were 0.76 (95%CI, 0.56–0.95) and 0.78 (95%CI, 0.60–0.96) with cutoffs of 31 cm/s and 40 cm/s, respectively. For none of the velocity parameters did the areas under the ROC curves differ significantly between the left and right sides. The best performance was obtained using mean systolic (SV) and a cutoff of 95 cm/s, which yielded a positive likelihood ratio of 3.8 and a negative likelihood ratio of 0.25.
Conclusion: Our preliminary results showed a significant association between increased TCD velocities and NCSE in comatose patients. However, the likelihood ratios suggested a limited role for TCD in helping to diagnose seizure activity. Further studies with larger samples of NCSE patients are warranted to determine the exact contribution of TCD for NCSE detection in comatose ICU patients.
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1. Introduction

Nonconvulsive status epilepticus (NCSE) is a heterogeneous and complex electro-clinical condition manifesting as behavioral and mental alterations combined with continuous epileptiform discharges.[1] In a study of comatose patients who had no clinical seizures, electroencephalography (EEG) showed NCSE in 8% of cases.[2] Up to 20% of patients with convulsive status epilepticus have persistent NCSE after treatment [3] and 44% of patients in post-anoxic coma have NCSE [4]. NCSE is a severe complication associated with high morbidity and mortality rates and must therefore be diagnosed promptly.[3,5–7]

EEG monitoring is the reference standard for diagnosing NCSE. However, EEG changes related to NCSE may be difficult to differentiate from those produced by other causes of coma, such as encephalopathy.[1] Therefore, additional investigations may be useful in comatose patients with suspected NCSE. The bispectral index has been used to diagnose seizures in a few patients but has not been evaluated in prospective studies.[8] Transcranial Doppler ultrasound (TCD) is a noninvasive investigation that can be easily performed in the intensive care unit (ICU) and that reliably detects cerebral blood flow (CBF) alterations by measuring blood velocities in the basal cerebral arteries, including the middle cerebral artery (MCA).[9]

As NCSE is associated with an increase in CBF,[10] we hypothesized that NCSE was associated with CBF changes that were detectable by TCD.[11–14] We assessed this hypothesis in a

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prospective observational study of the diagnostic accuracy of TCD for NCSE detection in comatose ICU patients. The reference standard was continuous EEG monitoring. We also measured optic nerve sheath diameter (ONSD) using ocular ultrasonography to detect increases in intracranial pressure. ONSD has been validated as a good surrogate for invasive intracran ial pressure measurement.[15–17]

2. Materials and methods

The ethics committee of the French Society for Critical Care approved this prospective observational study and waived the need for written informed consent.

2.1. Patients

Consecutive comatose adults admitted to our ICU between November 2009 and November 2011 were included prospectively if they required EEG and intracranial pressure monitoring. Patients with ocular trauma or a known history of ocular disease (e.g., glaucoma or cataract) were not included. We did not include patients in whom EEG, TCD, and ONSD could not be performed simultaneously.

2.2. Definitions

Coma was defined as a Glasgow Coma Scale (GCS) score lower than 9.[18] NCSE in comatose patients with or without subtle convulsive movements (rhythmic twitching of the arms, legs, trunk, or facial muscles; tonic eye deviation; or nystagmoid eye jerking)[19] was defined as EEG findings of continuous or recurrent epilepsy-like activity including rhythmic focal or generalized spikes, sharp waves, or rhythmic waves changing in amplitude, frequency, and/or spatial distribution[20] and lasting more than 5 min.

2.3. Investigations for causes of coma

After a careful history and thorough physical examinations on scene and at ICU admission, including neurological evaluations, investigations were performed as appropriate to identify the factors causing the coma. Laboratory tests were obtained routinely. Plasma anticonvulsant drug assays and qualitative tests for toxic substances or medications associated with coma were performed at the discretion of the attending physicians. Cerebral imaging and EEG monitoring were obtained routinely. Lumbar puncture was performed when there was a fever or clinical suspicion of meningitis and when deemed appropriate by the attending physicians. The primary cause of coma was classified as cardiac arrest, subtle status epilepticus, stroke, hypoglycemia, bacterial meningitis, hypoxemia, or traumatic brain injury.

2.4. Investigations for nonconvulsive status epilepticus

The reference standard for diagnosing NCSE was bipolar 8-channel continuous EEG monitoring (Neurosoft Neuron Spectrum 4, Neurosoft, Ivanovo, Russia), via scalp electrodes positioned according to the Standard International 10–20 system (Fp2-T4, T4-O2, Fp2-C4, C4-O2, Fp1-T3, T3-O1, Fp1-C3, and C3-O2). EEG monitoring was performed and interpreted by a qualified neurophysiologist (SL).

TCD (EnVisor CHD ultrasound machine, Philips, Amsterdam, The Netherlands) was performed routinely as previously described[9] by a single trained investigator (SM) in the minutes after EEG monitoring initiation.[17,21] TCD was first performed on the right and left MCAs through the temporal window as described by Aaslid et al.[9] Systolic (SV), end-diastolic (DV), and mean (MV) velocities were recorded. The pulsatility index (PI) was calculated as [PI = (SV − DV)/MV]. Maximal MCA PI was the left or right MCA PI value, whichever was higher, and mean MCA PI the mean of the left and right MCA PI values. Mean and maximal SVs and mean and maximal DVs were obtained in the same way.

Immediately after TCD measurements, the same investigator (SM) used the same ultrasound machine to measure ONSD 3 mm behind the ocular globe, inside the dura mater in the transverse and sagittal planes[15–17]; the mean value of these two measurements was defined as the ONSD for each eye.[16] Maximal ONSD was the left or right ONSD value, whichever was higher.

2.5. Management of comatose patients in the ICU

All patients received mechanical ventilation. Measures were taken to stabilize hemodynamics as needed. Hypoglycemia was looked for routinely and corrected if present. If glucose was given, 100 mg of thiamine was administered concomitantly, most notably when there was evidence of vitamin B1 deficiency. Patients were routinely evaluated for hyperthermia, hyperglycemia, hypo- or hypercarbia, anemia, metabolic disturbances, epileptic activity, and aspiration pneumonia; all such disorders were corrected promptly. When EEG monitoring showed NCSE, anesthetic drugs (propofol and/or midazolam and/or thiopental) were given in titrated doses to induce EEG burst suppression then as a continuous infusion for at least 12 h.[22]

2.6. Data collection

A standardized form was used to collect the variables listed in Tables 1–5. Severity and organ dysfunction at ICU admission were assessed using the simplified acute physiology score II (SAPS-II) and the logistic organ dysfunction (LOD) system score.

2.7. Statistical analysis

Quantitative parameters are reported as median (interquartile range [IQR]) and qualitative parameters as number (%). Categorical variables were compared using Fisher's exact tests and continuous variables using Wilcoxon rank-sum tests.

Median (IQR) stay lengths in the ICU and hospital were estimated using the reverse Kaplan–Meier approach. Median (IQR) mechanical ventilation duration was estimated with death as a censoring event.

Receiver-operating characteristic (ROC) curves were plotted to evaluate the performance of TCD and ONSD for detecting NCSE. The area under each ROC curve (ROC-AUC) was calculated and its 95% confidence interval (95%CI) was estimated as described by Delong and Delong. When ROC-AUC was greater than 0.6, several cutoffs were evaluated and the cutoff providing the best compromise between sensitivity (Se) and specificity (Sp) was identified. When several points were at the same distance from the ideal curve (Se = 1 and Sp = 1), priority was given to sensitivity. The positive and negative likelihood ratios (LR+ and LR−) obtained using the optimal cutoffs were calculated.

3. Results

Of 44 patients who met our inclusion criteria during the study period, 6 could not be enrolled because of an inadequate temporal bone acoustic window for TCD monitoring, leaving 38 patients for the final analysis.

Table 1
Patient characteristics and outcomes in the groups with and without nonconvulsive status epilepticus.

	N (%) or median (interquartile range)			
	All patients *n* = 38 (100)	Patients without NCSE *n* = 28 (73.7)	Patients with NCSE *n* = 10 (26.3)	*p* value
Demographics				
Male gender	29 (76.3)	22 (78.6)	7 (70.0)	0.67
Age (years)	56 (48–66)	55 (48–62)	62 (51–67)	0.27
SAPS II score at ICU admission	60 (52–73)	56 (51–68)	74 (60–85)	**0.03**
Patient characteristics and management at inclusion				
LOD score	7 (6–9)	7 (6–9)	8 (7–9)	0.24
Glasgow Coma Scale score	3 (3–3)	3 (3–3)	3 (3–4)	0.50
Heart rate (beats/min)	98 (75–107)	91 (69–107)	104 (88–114)	0.18
Mean arterial blood pressure (mm Hg)	92 (79–110)	92 (79–114)	91 (81–107)	0.50
Catecholamines, yes	19 (50.0)	14 (50.0)	5 (50.0)	1.00
Sedation, yes	28 (73.7)	19 (67.9)	9 (90.0)	0.24
Therapeutic hypothermia, yes	10 (26.3)	6 (21.4)	4 (40.0)	0.40
Temperature (°C)	36.6 (35.8–37.6)	36.5 (35.6–37.2)	37.6 (36.0–37.9)	0.13
Glycemia (g/L)	1.6 (1.1–2.4)	1.9 (1.1–2.4)	1.3 (1.0–2.5)	0.30
Natremia (mmol/L)	142 (140–144)	143 (140–144)	142 (139–144)	0.97
PaO_2 (mm Hg)	109 (86–140)	120 (81–175)	99 (87–111)	0.41
PCO_2 (mm Hg)	37 (33–42)	37 (33–42)	35 (32–43)	0.76
Outcomes				
Duration (days) of mechanical ventilation	6 (3–13)	6 (3–13)	NA	NA
Length (days) of ICU stay	15 (8–26)	15 (7–26)	NA	NA
Length (days) of hospital stay	20 (18–42)	19 (10–41)	NA	NA
Hospital mortality	21 (55.3)	12 (42.9)	9 (90.0)	**0.01**

Values of *p* in bold are significant ($p < 0.05$).
Abbreviations: NCSE, nonconvulsive status epilepticus; SAPS, simplified acute physiology score; ICU, intensive care unit; LOD, logistic organ dysfunction score. (NA) Estimates are not possible due to the small number of survivors.

Table 2
Tests to identify the cause of coma and results in the groups with and without nonconvulsive status epilepticus.

n (%)	All patients *n* = 38 (100)	Patients without NCSE *n* = 28 (73.7)	Patients with NCSE *n* = 10 (26.3)	*p* value
Tests to identify cause of coma				
Head CT scan	32 (84.2)	24 (85.7)	8 (80.0)	0.64
Brain MRI	9 (23.7)	7 (25.0)	2 (20.0)	1.00
Lumbar puncture	14 (36.8)	12 (42.9)	2 (20.0)	0.27
Causes of coma				0.89
Cardiac arrest	21 (55.3)	14 (50.0)	7 (70.0)	
Convulsive status epilepticus	10 (26.3)	8 (28.5)	2 (20.0)	
Stroke	1 (2.6)	1 (3.6)	0	
Hypoxemia	2 (5.3)	2 (7.1)	0	
Bacterial meningitis	2 (5.3)	1 (3.6)	1 (10.0)	
Hypoglycemia	1 (2.6)	1 (3.6)	0	
Traumatic brain injury	1 (2.6)	1 (3.6)	0	

Abbreviations: NCSE, nonconvulsive status epilepticus; CT, computed tomography; MRI, magnetic resonance imaging.

3.1. Baseline patient characteristics and ICU management

Patient characteristics are reported in Table 1. Median number of organ dysfunctions was 2 (IQR, 2–3). The main investigations performed to identify the causes of coma are listed in Table 2. Overall, at least one cause of coma was found in all 38 patients.

Table 3
Electroencephalography findings during transcranial Doppler and ocular sonography.

	n (%)
Suppression burst	10 (26.3)
Continuous	
Theta and/or delta rhythm	16 (42.1)
Electrical status epilepticus	
Generalized rhythmic bilateral spikes	9 (23.7)
Generalized rhythmic delta activity	1 (2.6)
Isoelectric	2 (5.3)

3.2. EEG

EEG identified NCSE in 10 (26%) patients (Table 3). Generalized rhythmic bilateral spikes were seen in 9 patients and generalized rhythmic delta activity in 1 patient.

3.3. Transcranial Doppler

Table 4 reports the TCD findings. Bilateral mean and maximal systolic and diastolic TCD velocities were significantly different between patients with and those without NCSE. The ROC curves for the diagnostic performance of NCSE are shown in Fig. 1, E2, and E3. ROC-AUC values for mean and maximal SVs with cutoffs of 95 cm/s and 105 cm/s, respectively, were 0.82 (95%CI, 0.64–1.00) and 0.79 (95%CI, 0.62–0.95) (Fig. 1). For mean and maximal DVs, cutoffs of 31 cm/s and 40 cm/s, respectively, yielded ROC-AUC values of 0.76 (95%CI, 0.56–0.95) and 0.78 (95%CI, 0.60–0.96) (Fig. 1). None of the ROC-AUC values differed significantly between the left and right

Table 4
Transcranial Doppler and ocular sonography findings in the groups with and without nonconvulsive status epilepticus.

	N (%) or median (interquartile range)			
	All patients *n* = 38 (100)	Patients without NCSE *n* = 28 (73.7)	Patients with NCSE *n* = 10 (26.3)	*p* value
Transcranial Doppler				
Left MCA PI	0.96 (0.82–1.26)	0.96 (0.82–1.21)	1.01 (0.82–1.51)	0.72
Right MCA PI	0.97 (0.87–1.23)	0.94 (0.87–1.25)	1.05 (0.84–1.18)	0.60
Mean MCA PI	0.96 (0.83–1.31)	0.94 (0.86–1.27)	1.03 (0.8–1.40)	0.96
Maximal MCA PI	1.05 (0.92–1.38)	1.01 (0.92–1.32)	1.10 (0.84–1.51)	0.73
Left SV (cm/s)	82 (54–118)	73 (52–104)	118 (106–168)	**0.02**
Right SV (cm/s)	75 (57–103)	65 (51–87)	117 (87–185)	**0.009**
Mean SV (cm/s)	77 (61–111)	70 (59–90)	116 (98–184)	**0.003**
Maximal SV (cm/s)	91 (66–118)	83 (64–108)	118 (108–185)	**0.008**
Left DV (cm/s)	30 (19–47)	25 (19–37)	46 (21–85)	**0.03**
Right DV (cm/s)	27 (20–45)	23 (18–35)	49 (30–96)	**0.02**
Mean DV (cm/s)	29 (19–44)	26 (18–36)	45 (32–92)	**0.02**
Maximal DV (cm/s)	35 (21–48)	31 (19–42)	49 (42–96)	**0.009**
Ocular sonography				
Left ONSD (mm)	5.8 (5.5–6.0)	5.8 (5.5–6.0)	5.9 (5.5–6.0)	0.96
Right ONSD (mm)	5.7 (5.4–6.0)	5.7 (5.3–5.9)	5.9 (5.4–6.0)	0.76
Mean ONSD (mm)	5.8 (5.4–6.0)	5.8 (5.4–5.9)	5.8 (5.6–6.0)	0.55
Maximal ONSD (mm)	5.9 (5.6–6.0)	5.8 (5.5–6.0)	5.9 (5.8–6.1)	0.52

Values of *p* in bold are significant ($p < 0.05$).
Abbreviations: NCSE, nonconvulsive status epilepticus; MCA, middle cerebral artery; PI, pulsatility index; SV, systolic velocity; DV, diastolic velocity; ONSD, optic nerve sheath diameter.

Table 5
Performance of transcranial Doppler mean and maximal systolic and diastolic velocity cutoffs in detecting nonconvulsive status epilepticus.

	Mean SV >95 cm/s	Mean DV >31 cm/s	Maximal SV >105 cm/s	Maximal DV >40 cm/s
Nonconvulsive status epilepticus prevalence = 26.3%				
Sensitivity	0.80	0.80	0.80	0.80
Specificity	0.79	0.68	0.75	0.75
Positive likelihood ratio	3.80	2.50	3.20	3.20
Negative likelihood ratio	0.25	0.29	0.27	0.27

Abbreviations: SV, systolic velocity; DV, diastolic velocity.

sides (Figure E2). The best performance was obtained using mean SV and a cutoff of 95 cm/s, which yielded an LR+ of 3.8 and an LR− of 0.25 (Table 5 and E1).

Mean cerebral artery PI values were not significantly different between the groups with and without NCSE (Table 4 and Figure E3).

3.4. Optic nerve sheath diameter

ONSD was abnormally high in the overall population, with a mean value of 5.8 mm (IQR, 5.4–6.0) and a maximal value of 5.9 mm (IQR 5.6–6.0). ONSD was not significantly higher in the group with NCSE than in the group without NCSE (Table 4).

4. Discussion

To our knowledge, this is the first study designed to evaluate the potential usefulness of transcranial Doppler for helping to diagnose NCSE in comatose patients. We found significant increases in systolic and diastolic cerebral blood flow velocities in patients with NCSE diagnosed by EEG. Mean SV had the best performance for detecting NCSE, with a cutoff value of 95 cm/s. Nevertheless, diagnostic performance was limited, even for mean SV, suggesting only an ancillary role for TCD as a tool for suspecting NCSE. Intracranial pressure as approached by ONSD measurement was raised in both groups. However, there was no statistical difference in ONSD measurement between patients with NCSE and those without NCSE. These findings are consistent with the included population – namely cardiac arrest, status epilepticus and bacterial meningitis – particularly at risk for raised ICP. Thus, the initial cause of coma, more than nonconvulsive status epilepticus itself, is likely to be responsible for the elevation of ONSD in our population.[23–26].

We studied patients at particularly high risk for NCSE, namely, comatose survivors of cardiac arrest; comatose patients with no further clinical seizures after treatment for convulsive status epilepticus; and various conditions associated with coma such as stroke, prolonged hypoglycemia, bacterial meningitis, prolonged hypoxemia, and traumatic brain injury. The 26.3% prevalence of NCSE diagnosed using EEG in our population reflects this high level of risk, which allowed us to evaluate a pragmatic strategy for NCSE detection in comatose ICU patients[3,5,7,27,28]. Lower prevalences were found in retrospective studies of unselected comatose patients.[2,29]

The use of TCD for detecting seizure activity is supported by the neurovascular coupling concept characterized by interactions between neuronal activity, metabolism, tissue and blood oxygenation, and blood flow.[30] According to this concept, seizure activity is associated with increases in metabolic rate and cerebral blood flow[11] that may be particularly marked in status epilepticus.[13] Experimental models of status epilepticus have documented cerebral hyperperfusion with cortical hyperemia in the ictal zone.[31] In vivo data that support the neurovascular coupling concept come from an interesting case report[32] and several neuroimaging studies.[33] More specifically, simultaneous EEG and functional MRI shows a blood oxygenation level-dependent (BOLD) signal during the epileptic discharge in the ictal area.[34]

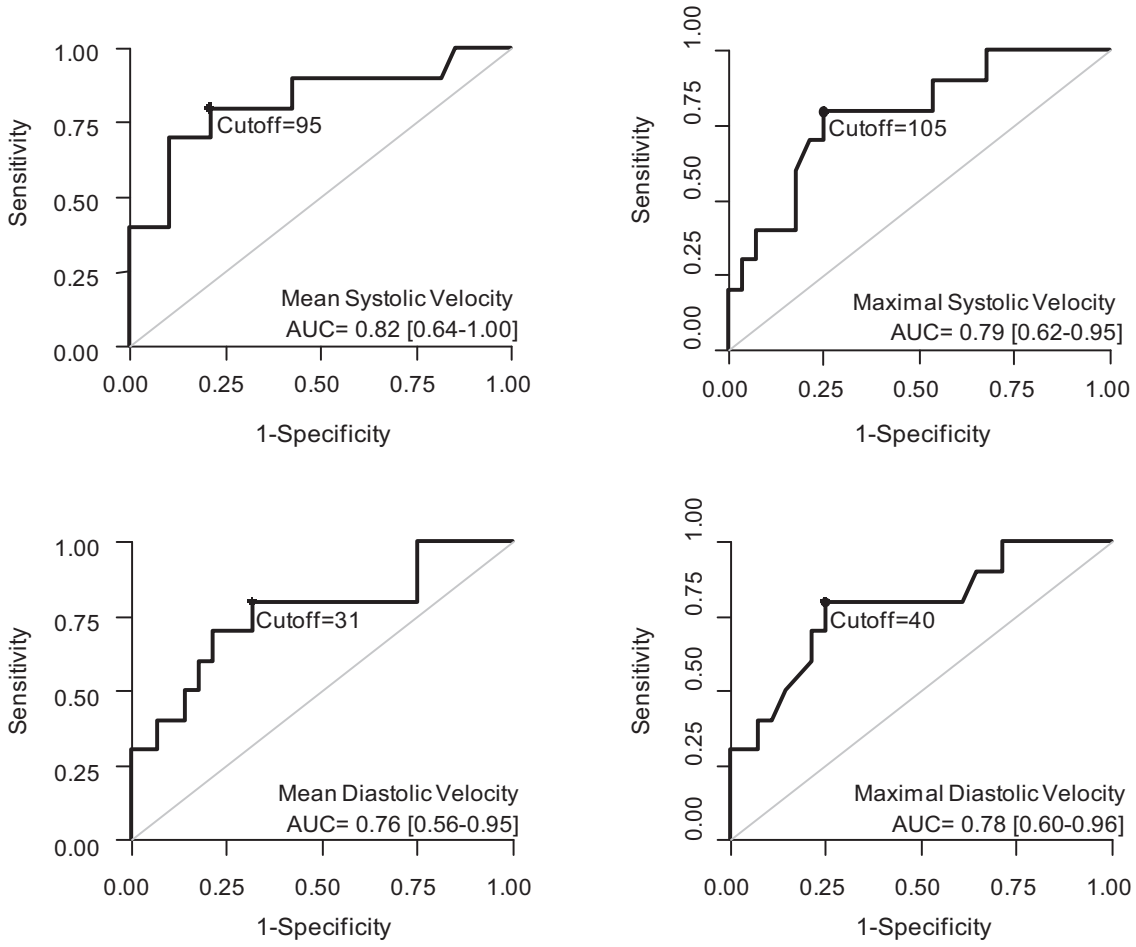

Fig. 1. ROC curves of the performance of mean and maximal systolic and diastolic velocities measured using transcranial Doppler in identifying nonconvulsive status epilepticus.

Most of the previous studies of TCD for detecting seizure activity were conducted during electroconvulsive therapy (ECT). Saito et al. first reported variations in mean blood flow velocities after electrically induced seizures.[35] Vollmer-Haase et al. showed that mean blood flow velocities increased dramatically after ECT, by more than 200%, and returned to baseline values within 2–6 min after ECT.[36] During a spontaneous simple partial motor seizure in an 11-year-old girl, blood flow velocity changes were documented in both MCAs and predominated on the side of the ictal focus.[37] In a larger series of 16 children with 33 EEG-recorded seizures, TCD monitoring identified an increase in MCA blood flow velocity of up to 191% of the basal value during tonic–clonic seizure activity. Surprisingly, blood flow velocities were unchanged in patients with NCSE, whereas mean velocities were decreased during absence seizures.[38]

In our population of comatose patients, all SVs and DVs were significantly associated with NCSE. As the EEGs showed generalized seizure activity, we focused on the mean and maximal SV and DV values. ROC curve analysis allowed us to determine that the best cutoffs were 95 cm/s for mean SV and 105 cm/s for maximal SV. Moreover, ONSD was not significantly different between patients with and without NCSE, indicating that the TCD velocity changes were probably not related to changes in intracranial pressure. To evaluate the diagnostic performance of TCD in our population with a high prevalence of NCSE, we computed LR+ and LR−. Although velocities differed significantly between the groups with and without NCSE, diagnostic performance was limited, indicating that TCD should be viewed as only an ancillary tool for alerting to the possibility of NCSE in comatose ICU patients. The diagnosis of NCSE should continue to rely on EEG monitoring.

Our study has several limitations. First, the applicability of our results to the full spectrum of ICU patients with NCSE is unclear. We included a relatively small number of patients at high risk for NCSE. The pre-test probability of having NCSE was high. The performance of TCD for detecting NCSE should be evaluated in different populations with different pre-test probabilities of having NCSE. The prevalence of NCSE in our comatose patients was higher than previously described.[2,29] However, many of our patients were comatose survivors of cardiac arrest or patients remaining comatose after control of clinical seizures due to convulsive status epilepticus. These two conditions are associated with a particularly high risk of NCSE, of up to 44%[4] and 20%[3], respectively. However, LR+ and LR− allow an assessment of diagnostic performance independently from the prevalence of the disorder to be diagnosed. Second, cerebral autoregulation is seriously compromised in patients with anoxic–ischemic encephalopathy. This affects blood flow relative to systemic blood pressure, but also affects the response of regional blood flow to changes in cerebral metabolism. Thus, the changes in CBF in response to seizures in may be less in anoxic–ischemic encephalopathy than in other conditions. Last, as previously reported, in 14% of patients eligible for the study TCD signal detection failed because of an inadequate of temporal bone acoustic window.[39]

In conclusion, our preliminary results show a significant association between increased TCD velocities and NCSE in comatose ICU patients. However, LR+ and LR− values indicated

limited diagnostic accuracy. Therefore, at this time the usefulness of TCD for helping to diagnose NCSE should be viewed with circumspection. Continuous EEG monitoring is the only way to detect NCSE in comatose patients. Further studies with larger samples of NCSE patients are warranted to determine the exact contribution of TCD for NCSE detection in comatose ICU patients.

Contributors

SL, SM and TG conceived, designed, and supervised the trial. All the investigators collected the data, and SL coordinated the data collection. MRR and CM analyzed and interpreted the data and were in charge of the statistical analysis. SL, SM, TG and MRR wrote the first draft of the paper. All authors approved the final version of the report.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

Collaborators (all in France)

The following collaborators participated in the study: Pierre Guezennec, Intensive care unit, CH André Mignot, Le Chesnay (78); Matthieu Henry-Lagarrigue, Intensive care unit, CH André Mignot, Le Chesnay (78); Julia Hilly-Ginoux, Intensive care unit, CH André Mignot, Le Chesnay (78); Virginie Laurent, Intensive care unit, CH André Mignot, Le Chesnay (78); Gilles Troché, Intensive care unit, CH André Mignot, Le Chesnay (78); Fabrice Bruneel, Intensive care unit, CH André Mignot, Le Chesnay (78); Benjamin Planquette, Intensive care unit, CH André Mignot, Le Chesnay (78); Pierrick Cronier, Intensive care unit, CH André Mignot, Le Chesnay (78); David Schnell, Intensive care unit, CHU Saint Louis, Paris (75); Mohamed Srairi, Pôle Anesthésie Réanimation, Centre Hospitalier Universitaire de Toulouse, 31059 Toulouse.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2014.01.001.

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